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Onset of Ocular Graft-versus-Host Disease Symptoms after Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract

Objective—To study the factors affecting the time to onset of ocular GVHD in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Methods—A retrospective chart review of 200 patients with ocular GVHD was performed to evaluate the association between various donor-recipient characteristics on the time to onset of ocular GVHD after allo-HSCT.

Results—The median time to onset of chronic ocular GVHD after allo-HSCT was 293 days (range 26 to 2308). Patients receiving fully HLA-matched transplants had a delayed onset of ocular GVHD (median 294 days) compared to mismatched transplants (219 days; P=0.029). HLA-matched transplants from related donors had delayed onset of ocular GVHD (307 days) compared to HLA-matched (286 days; P=0.168) and HLA-mismatched (231 days; P=0.015) transplants from unrelated donors. Ocular GVHD followed systemic GVHD in 76% of patients but preceded systemic disease in 7%, occurred concurrently in 15%, and was not associated with systemic GVHD in 2% of patients. The time elapsed between the occurrence of systemic and ocular GVHD was significantly longer in matched-related transplants (250 days) than in matched-unrelated transplants (120 days; P=0.004).

Conclusion—The onset of ocular GVHD after allogeneic hematopoietic stem cell transplantation is variable and is influenced by the donor-recipient matching characteristics. In the majority of patients with GVHD ocular involvement follows the occurrence of systemic manifestations; however, importantly, it can also precede or develop independently of systemic disease in a minority. Regular ophthalmic follow-up is recommended after allo-HSCT regardless the concurrent systemic GVHD status.

Keywords

Ocular graft-vs-host disease; dry eye; allogeneic hematopoietic stem cell transplant

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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an established therapeutic modality for neoplastic and non-neoplastic hematological disorders. Improvements in human leukocyte antigen matching as well as advances in pre- and post-transplant regimens have increased the number of patients receiving this therapy.[1,2] Newer therapeutic approaches, assisted by better supportive care, have helped enhance survival during the post-transplant period.[3] This has, however, led to emergence of complications due to prolonged patient survival. Graft-versus-host disease (GVHD) is a common cause of morbidity and mortality after HSCT.

The incidence of ocular GVHD is 40-60% in patients receiving allo-HSCT.[4,5] The incidence of chronic ocular GVHD occurring within 3 years of transplantation in adults and children is widely variable and ranges from 30-85%.[6] Historically, ocular GHVD has been considered to be a manifestation of extensive systemic GVHD that includes signs and symptoms of dry eye.[7] Symptoms of chronic ocular GVHD are irritation, burning, pain, redness, grittiness, foreign-body sensation, excessive tearing, sensitivity to light and blurred vision; these symptoms impair quality of life and activities of daily living.[8] Clinical findings of the ocular surface in GVHD may include acute conjunctival inflammation, conjunctival hyperemia and chemosis, pseudomembranous and cicatricial conjunctivitis, severe corneal epitheliopathy, filaments, painful erosions, corneal ulceration, perforation and scarring.[9]

There are high concordance rates between acute and chronic systemic GVHD, and acute GVHD has been shown to be a strong predictor of chronic GVHD. One study reported that patients with acute GVHD had a greater risk of chronic GVHD.[10] As a result; risk factors for acute GVHD may by extension apply to chronic GVHD. Studies have demonstrated a strong association between dry eye and both acute and chronic systemic GVHD.[11,12] Risk factors for the subsequent development of ocular GVHD include skin and mouth involvement, peripheral blood stem cell transplantation, male donor to female recipient and a history of acute GVHD.[7,8]

One review showed that limited effect of treatments for ocular GVHD can sometimes be a consequence of patients presenting at an advanced stage of the disease, when permanent damage to the tissues is already present.[13] The objective of this study was to evaluate the time elapsed from allo-HSCT to the onset of ocular GVHD and to identify its associated factors, which would allow for monitoring patients at risk leading to earlier diagnosis and management.

Materials and Methods

This was a retrospective study from records of post allo-HSCT patients presenting with ocular GVHD at the Cornea Service, Massachusetts Eye and Ear Infirmary (MEEI), between May 2007 and September 2011. Approval was obtained from the MEEI Institutional Review Board, and the study was carried out following the tenets of the Declaration of Helsinki. The records of 200 post allo-HSCT patients, flagged as oncology protocol patients and presenting for evaluation of dry eye and ocular surface inflammation, were reviewed. Details about allo-HSCT and diagnosis of non-ocular systemic GVHD, reported by the oncology team, were obtained from the electronic medical records. All patients included in

the final analysis underwent transplantation at the Harvard Cancer Center affiliated hospitals (Dana-Farber Cancer Institute and Massachusetts General Hospital, Boston, MA). Chronic ocular GVHD was diagnosed in patients who presented with all of the following: 1) history of allogeneic HSCT, 2) exclusively post-HSCT self-reported onset of dry eye symptoms including irritation, burning, dryness or foreign body sensation (OSDI score >33) that required treatment with frequent topical lubricants or anti-inflammatory eye drops, 3) signs of ocular surface disease which included any two of the following: decreased Schirmer test (≤5mm), presence of corneal fluorescein staining (CFS; modified oxford scale) and decreased tear beak-up time (TBUT; ≤10 seconds) confirmed by a cornea specialist. Most patients presented with a previous diagnosis of systemic GVHD, and were diagnosed with *definite* ocular GVHD, while patients without a previous diagnosis of systemic GVHD were diagnosed as *probable* ocular GVHD. For the purpose of our analyses, patients with diagnoses of definite and probable ocular GVHD were combined.

The onset of ocular GVHD was defined by the date of the first patient's report of symptoms entered in the medical records, provided that the presence of ocular signs was later confirmed at the MEEI Cornea Clinic. The time (days) elapsed between the transplant and onset of ocular GVHD was analyzed for all the patients as well as in different subgroups defined by donor-recipient match characteristics. The subgroups analyzed were defined by the donor status as follows: genotypically identical siblings or other related 6/6 HLA-match (matched-related) donor, matched-unrelated donor, and 5/6 HLA-match (mismatched-unrelated) donor. The time elapsed between the onset of systemic GVHD and the diagnosis of ocular GVHD was also analyzed. Additionally, we calculated the time elapsed from HSCT to the onset of ocular GVHD in different groups defined by: donor-recipient gender mismatch (male donor to female recipient, female donor to male recipient) status, conditioning and prophylactic regimens, recipient age, and involvement of systemic organs. We excluded patients with incomplete records regarding details of their HSCT. Patients with other ocular conditions such as, but not limited to, herpetic eye disease, scleritis, episcleritis and glaucoma (using multiple anti-glaucoma medications), which may confound the diagnosis of ocular GVHD were also excluded.

Statistical Analysis

Data are presented as the mean or median ± standard deviation (SD) and range for continuous variables, and percentages for categorical variables. Because of the non-normal distribution of some of the data, presenting the median reflects a more accurate figure of the actual data. We used the Mann-Whitney U test for 2-sample analysis and the Kruskal-Wallis test, including post-hoc tests for multiple comparisons. A two-sided P value <0.05 was considered statistically significant.

Results

The final analysis included 179 patients (98 male and 81 female), with a mean age of 49±12 years (range 19 to 73). All patients included in the analysis underwent allo-HSCT between July 1996 and July 2011 and were diagnosed with ocular GVHD between August 1997 and August 2011. Patients included in the study were found to have a mean OSDI score of 50.8

(±25.1), mean Schirmer's score of 5.4 mm (SD, ±5.1), mean CFS of 1.7 (±1.2) and mean TBUT of 3.3 (±2.6). The median time elapsed from transplantation to onset of chronic systemic GVHD was 175 days (6 to 1477) The median time elapsed from transplantation to onset of chronic ocular GVHD was 293 days (26 to 2308 days). In 14 patients (8%), ocular GVHD developed within the first 100 days after transplantation, and, by one year, 114 patients (64%) had developed ocular GVHD.

In our cohort, the recipients of matched-related transplants had a delayed onset of ocular GVHD (median 307 days) compared to recipients of matched-unrelated transplants (286 days) and recipients of mismatched-unrelated transplants (231 days). The difference between matched-related and mismatched-unrelated groups was statistically significant (P=0.015) (Table 1). When pooling the groups by HLA match, the group of patients with a 5/6 matched transplant (mismatched; n=29) had a statistically significantly shorter time to onset of ocular GVHD (219 days) than the group of patients with fully matched donors (294 days; n=150; P=0.029).

In our series, ocular GVHD developed in patients with a previous diagnosis of systemic GVHD in 76% of the cases (136 patients). In this group, individuals with matched-unrelated transplants developed ocular GVHD earlier after the HSCT (296 days) than recipients of matched-related transplants (378 days; P=0.036). Likewise, the period elapsed between development of systemic and ocular GVHD in individuals with matched-unrelated transplants was shorter (120 days) than in individuals receiving matched-related transplants (250 days; P=0.004) (Table 2). Systemic GVHD that followed ocular GVHD presented only in 7% of the cases (13 patients). Systemic and ocular GVHD occurred simultaneously in 15% of the cases (27 patients), and isolated ocular GVHD was present only in 2% of cases (3 patients).

There were no statistically significant differences regarding the time to onset of ocular GVHD among groups defined by the donor-recipient gender-matching status. Other typically known predictive factors for developing GVHD, such as conditioning therapy, medications used for prophylaxis, age of recipient and systemic organ involvement, did not affect time to onset of ocular GVHD in the population studied (Table 3).

Discussion

In the studied population, the median time to onset of ocular GVHD after bone marrow transplantation was 293 days. There are varying reports on the median time to onset of ocular GVHD after allo-HSCT, one study reported a median of 171 days in 53 patients, while another group reported a mean of 13.8 months (414 days) in 48 patients.[14,15] A possible reason for differences among these reports could be the absence of universally accepted diagnostic criteria for ocular GVHD, since the grading and diagnosis of GVHD continues to retain some subjective aspects. The National Institutes of Health (NIH) Working Committee on Chronic GVHD has published criteria for diagnosis of ocular GVHD based on positive Schirmer test and other accompanying distinctive features.[1] However, the Schirmer score can be unreliable in patients with dry eye disease as well as in patients with ocular GVHD.[14,16] For instance, the NIH system for grading severity of ocular

GVHD (based on the dry eye symptoms affecting activities of daily living and number of eye drops required per day) was developed to facilitate the diagnosis of ocular disease by non-ophthalmologists (e.g. oncologists). However, it is limited by ambiguity and exclusion of objective clinical signs. Other grading systems proposed for ocular GVHD rely exclusively on clinical findings without accounting for patient symptoms.[17,18] Furthermore, ocular complications as a consequence of total body irradiation, chemotherapy, immunosuppressive therapy, and signs of infections and meibomian gland dysfunction, may confound the diagnosis of ocular GVHD.[15,19]

As per the currently implemented NIH diagnostic criteria for systemic GVHD, ocular GVHD is considered “distinctive” but not “diagnostic”, and is insufficient by itself, to establish a diagnosis of GVHD; meaning that a systemic (non-ocular) diagnosis of GVHD is required before a definitive diagnosis of ocular GVHD can be made.[1] Three-quarters of the population in this study developed ocular GVHD after systemic GVHD, however, 7% of patients were diagnosed with systemic disease up to 2 years *after* the onset of ocular disease, which is in agreement with the other reports.[7, 14] In this study we found that 2% of patients developed isolated ocular GVHD in the absence of systemic GVHD; however, in a previous report the proportion was 12%.[13] Others have reported up to 38% of patients presenting with GVHD-associated dry eye in the absence of systemic GVHD.[20] Consequently, excluding patients with no prior history of systemic GVHD may lead to overlooking a diagnosis of ocular GVHD, which may manifest simply as acute onset of dry eye disease. In patients with a previous diagnosis of systemic GVHD attributing ocular symptoms to GVHD is apparent. However, in the absence of systemic GVHD findings (e.g. skin, liver, gut disease), signs and symptoms of ocular GVHD may be attributed by clinicians to non-HSCT related dry eye, with a resultant delay in aggressive management of the ocular surface disease. This is a critical point, as our group as well as others have documented the potential for rapid progression of ocular surface disease in these patients, including unilateral or bilateral corneal perforation, emphasizing the need for aggressive management of “dry eyes” in patients with HSCT.[21,22]

A disparity in major and/or minor HLA antigens is a major risk factor in the development of GVHD.[23-25] Transplantation from HLA-matched but unrelated donors has been shown to result in a higher incidence of acute systemic GVHD.[26-32] The findings of the present study show that patients who received mismatched transplantations developed ocular GVHD earlier than those who received fully matched transplants. However, one report found no association of HLA compatibility and dry eye after stem cell transplantation, while other reported a higher prevalence of ocular GVHD in related donor recipients.[33,34] Inconsistencies in the published literature may be explained by modifications in the type and duration of GVHD prophylaxis, due to continuous advances in transplant medicine, given to mismatched transplant recipients.[35] Additionally, most studies evaluating GVHD are retrospective, spanning various standards of care generations, include heterogeneous patient populations, and do not use consistent diagnostic and staging criteria.

Limitations of the present study are largely related to its retrospective design. Patients referred by their primary ophthalmologists or hematologists with a diagnosis of ocular GVHD were included in this study. We would like to emphasize of the extraordinary

difficulties for the ophthalmologist to follow-up patients with GVHD. These are in many cases extremely ill individuals who are usually followed up in oncology or internal medicine departments, and usually have a variety of systemic manifestations resulting in frequent hospitalization or mortality, which may lead to variable follow-ups to an eye clinic. The study population included only patients that presented ocular GVHD rather than including all patients undergoing bone marrow transplantation, thus we were unable to derive direct incidence data. The possibility of a recall bias by patients when addressing the exact onset of dry eye symptoms could have also been present. Additionally, the inability to evaluate patients at specific time points after transplantation can result in a later diagnosis of ocular GVHD than if evaluated prospectively at high frequency.

In conclusion, our results suggest onset of chronic ocular GVHD around one year post-transplant and support the need for frequent follow-up exams. After the onset of systemic GVHD, patients receiving transplants from unrelated donors tend to progress to ocular GVHD earlier than those from related donors. In addition, given the high risk for the occurrence of ocular GVHD in post-HSCT patients, it is important to consider that this disease may develop even several years after the transplant. Finally, it is important to emphasize that patients undergoing allogeneic hematopoietic stem cell transplantation may develop severe ocular surface disease as a manifestation of graft-versus-host disease without concurrent or preceding history of systemic manifestations of the disease.

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Table 1

Time Between Hematopoietic Stem Cell Transplant and Onset of Ocular GVHD

Donor-Recipient Characteristics	No. (%)	Median time between Allo-HSCT and ocular GVHD in days (months)	Range (Days)	Interquartile range (Days)
5/6 HLA-match	29 (16)	219 (7)	26-621	153-348
6/6 HLA-match	150 (84)	294 (10)	28-2308	223-506
Matched-Related	66 (36.9)	307 (10)	87-2308	241-577
Matched-Unrelated	84 (47.0)	286 (9)	28-1418	207-447
Mismatched-Unrelated	28 (15.6)	231 (8)	26-621	153-348
Mismatched-Related	1 (0.5)	-	-	-

GVHD = Graft-versus-host disease; HLA = Human Leucocyte Antigen; Matched = 6/6 HLA match; Mismatched = 5/6 HLA-match

Table 2

Time Between Onset of Systemic GVHD and Ocular GVHD in Patients Developing Ocular GVHD after Systemic GVHD

Donor-Recipient Characteristics	No. (%)	Median time between onset of systemic GVHD and Ocular GVHD in days (months)	Range (Days)	Interquartile range (Days)
Matched-Related	50 (37)	250 (8)	4-1845	113-512
Matched-Unrelated	67 (49)	120 (4)	7-1393	41-279
Mismatched-Unrelated	18 (13)	117 (4)	5-531	51-292

GVHD = Graft-versus-host disease; Matched = 6/6 HLA-match; Mismatched = 5/6 HLA-match

Table 3

Time to onset of ocular GVHD based on Age, Gender, Conditioning regimen. Systemic GVHD and GVHD prophylaxis.

	Number of patients	Median time to onset of ocular GVHD in days	95% Confidence interval	Interquartile range
Age				
≤50 years	94	277	328-483	217-507
>50 years	85	303	311-427	193-447.5
Gender Match				
Female to Female	27	251	234-361	200-336
Female to Male	33	363	347-639	246-634.5
Male to Male	46	279	304-498	209.5-505.5
Male to Female	56	293.5	252-402	139-435
Gender disparity	79	293	321-471	189-513
No Gender disparity	83	282	298-435.6	201-448
Conditioning Regimen				
TBI-based	70	306	345-529	240.5-543
Chemotherapy alone	109	275	302-411	184-435
Chronic GVHD				
Skin	140	279	317-426	198-447.5
Oral	117	279	335-464	212.5-412
Liver	78	293	334-466	224.5-519
GI	40	308	323-432	197.5-518.5
GVHD Prophylaxis				
MTX+TAC	55	272	259-432	173-419
MTX+TAC+SIR	41	282	281-408	223.5-380
MTX+TAC+Bortezomib	7	300	167-477	175-461
MTX+CSa	6	431	246-647	258.5-650
TAC+SIRO	40	334	361-595	239-612
TAC+SIRO+MMF	6	307	(−)254.1-1491	212-1337
TAC+MMF	3	132	31-208	n/a
Others	21	264	244-541	187-575.5

TBI = Total Body Irradiation; MTX = Methotrexate; TAC = Tacrolimus; SIR = Sirolimus; CSa = Cyclosporine; MMF = Mycophenolate Mofetil